REMARKS

By way of the above amendment, Applicant has amended claims 1, 5, 6 and 27. Applicant has submitted new claims 28-39. Claims 8-24 and 27 are cancelled.

The support for the amendment to claim 1 may be found in reference to page 10, lines 7-9, of the specification along with the GFP 3D structure as set forth in Applicant's Figure 7.

Claims 3-5 stand rejected under 35 USC §112 first paragraph as containing subject matter that was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicant respectfully requests reconsideration by the Examiner in light of the amended claims and the remarks which follow.

The Examiner has acknowledged that Applicant's specification provides the crystal structure for green fluorescent protein as set forth on page 10, lines 6-9. Applicant respectfully submits that a skilled artisan knowledgeable of fluorescent proteins would know that the modified fluorescent proteins including GFPs, BFPs, CFPs, YFPs, and DsRed fluorescent proteins are in fact mutants and/or share highly conserved crystalline structures found in the green fluorescent proteins. Each variant listed shares a basic crystal structure in common with the green fluorescent protein, namely an 11-stranded β-barrel formed from 11 β-sheets surrounding a chromophore-containing co-axial α-helix, each of said β-sheets forming said β-barrel being joined by a loop structure to at least one other β-sheet forming said β-barrel.

The common structure referenced above for the various fluorescent proteins was extremely well known at the time of the filing date of the present application. In support of this, Applicant is supplying copies of the following publications and or abstracts that are briefly commented upon below:

Heim, R. *et al.*, "Engineering green fluorescent protein for imporved brightness, longer wavelengths and fluorescence resonance energy transfer." Curr Biol. 1996 Feb 1:6(2): 178-82; PMID: 8673464

Dority & Manning, PA
P O Box 1449
Greenville, SC 29602-1449
(V) 864 271 1592
(F) 864 233 7342

Ormo M *et al.*, "Crystal structure of the Aequorea victoria green fluorescent protein." Science. 1996 Sep 6; 273(5280): 1392-5; PMID: 8703075

Yang F *et al.*, "The molecular structure of green fluorescent protein." Nat Biotechnol. 1996 Oct; 14(10): 1246-51; PMID: 9631087

Wachter RM *et al.*, "Crystal structure and photodynamic behavior of the blue emission variant Y66H/Y145F of green fluorescent protein." Biochemicstry. 1997 Aug 12;36(32):9759-65; PMID: 9245407

Yarbrough D *et al.*, "Refined crystal structure of DsRed, a fluorescent protein from coral, at 2.0-A resolution." Proc Natl Acad Sci USA. 2001 Jan 16;98(2):462-7; PMID: 11209050

Many of these references were set forth in Applicant's specification. The collective teachings indicate to one having ordinary skill in the art the structural similarities of the claimed and discussed fluorescent proteins. For instance, the Ormo et al reference confirms the structure of "an 11-stranded, β-barrel with a co-axial α-helix, with the chromophore forming from the central helix" with this reference being cited in Applicant's page 10, first full paragraph. Applicant's specification additionally cites the Yang et al reference which confirms the structure of GFP which addresses that a number of mutants are known which exhibit blue-shift and red-shift excitation and emission maxima. The Wachter et al (1997) disclosure clearly sets forth the standard GFP structure on page 9765, col. 1, lines 6-11, and confirms that the GFP structure and variants were well known as of Applicant's filing date.

The remaining enclosed abstracts and search results from the Protein Data Bank provide ample evidence that various fluorescent proteins listed in claim 6 have x-ray refraction properties which were well known in the art and were available through deposit agreements with the Protein Data Banks. As such, Applicant respectfully submits that one having ordinary skill in the art, and upon reading Applicant's specification, would be aware that all the identified fluorescent proteins would have loop structures in adjacent β-sheets similar to the crystal structure of GFP as described and illustrated in Applicant's specification.

Dority & Manning, PA
P O Box 1449
Greenville, SC 29602-1449
Voice: 864-271-1592
Fax: 864-233-7342

To the extent the Examiner relies upon the Branden et al reference, Applicant respectfully submits that this 1991 reference no longer represents the state of the art with regard to crystal structures. As the more recently submitted publications establish, the x-ray crystal structure for the proteins of interest are readily available along with the physical material from the various indicated depositories.

In summary, Applicant respectfully submits that the accompanying materials and explanation makes clear that one having ordinary skill in the relevant art would be aware of the overlapping structural similarity between the green fluorescent proteins as identified in Applicant's specification along with the additional fluorescent proteins which were also listed in Applicant's specification. Given the β-sheet structure shared by all the claimed fluorescent proteins, Applicant respectfully submits that the specification is enabling for Applicant's claimed invention. It should be noted that Applicant's specification sets forth multiple examples of green fluorescent proteins which were successfully modified and which fall within the scope of the claims. Given the skill level, prior knowledge within the art, and the ready availability of the crystal structures of the fluorescent proteins, Applicant respectfully submits that the rejections under 35 USC §112 first paragraph are now traversed.

With respect to the rejections under 35 USC §112 second paragraph, Applicant respectfully submits that the amended and new claims overcome these rejections.

Original claims 1, 2, 7, 25, and 26 are rejected under 35 USC §102(b) as being anticipated by Xu et al. Applicant respectfully submits that, as amended, Applicant's claimed invention is not anticipated by the Xu et al reference. The Xu et al reference teaches a cleavage site different from that set forth in Applicant's claimed invention. For instance, Xu et al teaches a linkage of two different fluorescent proteins, i.e., a green fluorescent protein and a blue fluorescent protein joined by a peptide. The synergy between the closely linked fluorescent proteins is affected by a protease cleavage resulting in alterations in the emission and excitation spectra. Applicant's invention as set forth in claims 1 and 28 is directed to a different location of a cleavage site. Further, claims 1, and 28 are directed to a single chromophore fluorescent protein as opposed to two different color chromophores joined by a cleavable peptide. As such,

Dority & Manning, PA
P O Box 1449
Greenville, SC 29602-1449
Voice: 864-271-1592
Fax: 864-233-7342

Applicant respectfully submits that the presently claimed invention is not anticipated or otherwise rendered unpatentable by the Xu et al reference.

In paper number 6, the Examiner stated that claims 5, 6, and 7 are generic to a plurality of disclosed patently distinct species. In response, Applicant was required to elect a single disclosed species for examination. Upon allowance of a generic claim, Applicant is entitled to have the restricted species added by way of a dependent claim or by way of an independent claim setting forth all the limitations of the dependent claim and intervening claims. It is in this regard that Applicant directs the Examiner's attention to claims 6, 36, 37, 38, and 39 which include the protein species which had been withdrawn for the purposes of examination.

Inasmuch as all outstanding issues raised by the Examiner have been addressed, it is respectfully submitted that the present application is in condition for allowance, and action to such effect is earnestly solicited. The Examiner is encouraged to telephone the undersigned at his/her convenience should only minor issues remain after consideration of the present Amendment, to permit early resolution of same.

Please charge any additional fees required by this Amendment to Deposit Account No. 04-1403.

Respectfully submitted,
DORITY & MANNING, PA

J. Bennett Mullinax
Reg. No. 36,221

Dority & Manning, PA
P O Box 1449
Greenville, SC 29602-1449
Voice: 864-271-1592
Fax: 864-233-7342

MARKED UP CLAIMS COPY

1. (Amended) A fluorescent protein comprising an 11-stranded β-barrel formed from 11 β-sheets surrounding a chromophore-containing co-axial α-helix, each of said β-sheets forming said β-barrel being joined by a loop structure to at least one other adjacent β-sheet forming said β-barrel modified such that said modified fluorescent protein incorporates a cleavage site for a protease, cleavage of said modified fluorescent protein at said cleavage site by said protease causing the alteration of at least one of the emission and excitation spectra of said modified fluorescent protein.

4. (Amended) A fluorescent protein according to claim 3, said [pair of] adjacent β-sheets being selected from the group consisting of β-sheet[s] pairs numbers 9 and 10, 5 and 6, and 8 and 9.

5. (Amended) A fluorescent protein according to claim 3, said modified fluorescent protein [being selected from any one of the group consisting D9, MD9, D4, D7, D8, E2, E3-1, E3-5, E3-9, E3-12, E4-a, E4-g, E4-j, E4-o and E4-p.] having SEQ. ID NO: 41.

6. (Amended) A fluorescent protein according to claim 1, being selected from any one of the group consisting [BFP, CFP, YFP and DsRed.] of a blue fluorescent protein, a cyan fluorescent protein, a yellow fluorescent protein, and a DsRed fluorescent protein.

7. (Amended) A fluorescent protein according to claim 1, said cleavage site having the sequence of [any one of the group consisting] SEQ ID NO[s]: 4 [and 7-13].

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